IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: E. BOMBARDELLI et al.

Application No.: 10/075,625 Group Art Unit: 1614

Filed: February 15, 2002 Examiner: To be assigned

For: CHALCONE COUMARINS Attorney Docket No.: 7914-088

SUBMISSION OF PRIORITY DOCUMENT

Assistant Commissioner for Patents
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Sir:

Applicant has claimed priority of Great Britain Patent Application No. 9920908.2, filed September 3, 1999 in Great Britain, under 35 U.S.C. § 119. In support of this claim, a certified copy of said patent application is submitted herewith.

No fee is believed to be due for this submission. Should any fees be required, however, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150., please charge such fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date October 22, 2002

Paul E. Dietze (Reg. No. 30,256)
For Victor N. Balancia (Reg. No. 31,231)

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EnclosureS

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NP10 8QQ

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9920908.2

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1/77

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The Patent Office

Cardiff Road
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1. Your reference — SDR\KYW\21414 GB

2. Patent application number
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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Indena S.p.A.
Viale Ortles, 12
20139 Milan
Italy

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — ITALY

02147781

4. Title of the invention — Chalcone coumarins

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

MATHYS & SQUIRE
100 Grays Inn Road
London WC1X 8AL

Patents ADP number *(if you know it)* — 1081001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

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Description	20
Claim(s)	7
Abstract	1
Drawing(s)	0

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Priority documents	-
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
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11. I/We request the grant of a patent on the basis of this application.

Signature

Date 3 September 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

Stephen D. Ritter 0171 830 0000

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The Patent Office

Statement of inventorship and of right to grant of a patent

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

   SDR/KYW/21414 GB

2. Patent application number
   (if you know it) 9920908.2

3. Full name of the or of each applicant

   Indena S.p.A.
   Viale Ortles, 12
   20139 Milan, Italy

4. Title of the invention

   Chalcone coumarins

5. State how the applicant*(s)* derived the right from the inventor*(s)* to be granted a patent

   Inventors are employees of applicant company

6. How many, if any, additional Patents Forms 7/77 are attached to this form?
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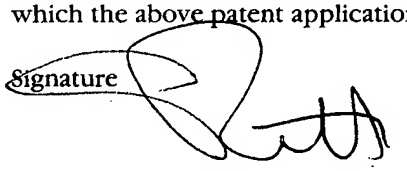
7. I/We believe that the person*(s)* named over the page *(and on any extra copies of this form)* is/are the inventor*(s)* of the invention which the above patent application relates to.

   Signature  Date 8.11.99

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   Stephen D. Ritter
   0171 830 0000

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Enter the full names, addresses and postcodes of the inventors in the boxes and underline the surnames

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Patents ADP number *(if you know it)*:

Reminder

Have you signed the form?

CHALCONE COUMARINS

The present invention relates to a novel class of compounds which have structures related to certain naturally occurring and synthetic chalcones, as well as to methods for the preparation of such compounds and to pharmaceutical uses thereof.

The compound 1,3-diphenyl-2-propene-1-one is known by the trivial name chalcone. Many naturally occurring flavonoids share structural features with chalcone and are referred to by the generic term "chalcones". Also, certain flavonoids, including ones which are also classified as chalcones, have recently been demonstrated to have anticancer activity (Cancer Research 48, 5754, 1988) and chemopreventive activity in some tumours (J. Nat. Prod. 53, 23, 1990).

In particular, quercetin, an ubiquitous flavonoid found in plants, has been shown to act on the proliferation of human leukemic cells (Br. J. of Haematology, 75, 489, 1990) and on other cell lines (Br. J. Cancer 62 94, 942, 1990; Int. J. Cancer, 46, 112, 1990; Gynaecologic Oncology, 45, 13, 1992) and to possess a synergic action with common antiblastic drugs.

In addition, some natural or synthetic chalcones, described in our International Patent Publication No. WO 9117749 and in International Patent Publication No. WO 96/19209 (Baylor College of Medicine) have proved to have a significant antiproliferation activity on a variety of different cell lines.

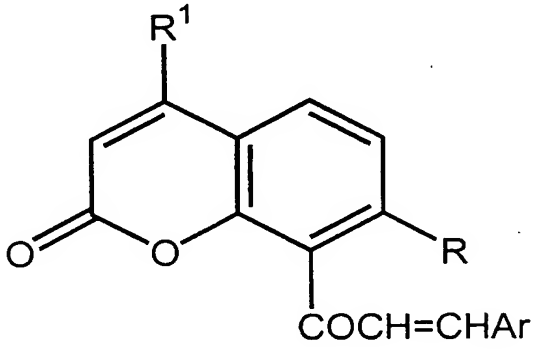
Although the mechanism of action of the antiproliferative activity of flavonoids and chalcones is still unknown, it is believed to be linked to the interaction of these compounds with type II estrogen receptors.

The action *in vivo* of these polyphenol substances is certainly much more complicated. All these compounds are generally characterised by an almost

complete insolubility in water and, *in vivo,* by a very poor bioavailability linked to a rapid metabolism of phenols and a marked affinity for lipids and proteins.

Surprisingly, it has now been found that certain novel chalcones, chalcone derivatives and chalcone analogues, in particular ones in which the phenyl ring in the 1-position is substituted or replaced by rings containing one or more heteroatoms, possess a greater antiproliferation activity both on sensitive cancerous cells and on cells which are resistant to common chemotherapeutic drugs, including the latest generation anti-neoplastic agents, pacitaxel and docetaxel.

Thus according to one aspect of the present invention, there are provided compounds of the general Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents:

a substituted or unsubstituted, (preferably aromatic), carbocyclic or heterocyclic group, said carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl,

(k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents

OH, OR^{10} or $OCOR^{11}$, wherein R^{10} and R^{11} are as defined above; and

R^1 represents H or a lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

A preferred class of compounds of Formula (I) are those wherein Ar represents a substituted or unsubstituted (preferably aromatic), heterocyclic group said heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, the heteroatoms being selected from N, O and S, and any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl (preferably R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl), (k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group.

In a preferred class of compounds, Ar contains a basic nitrogen function, for example,

by virtue of a heterocyclic nitrogen ring atom being present, or Ar may contain a substituent having a basic nitrogen, such as an amine, or an acetamido function. Thus accordingly, the Ar group is preferably a substituted or unsubstituted (preferably aromatic), heterocyclic group, said heterocyclic group containing from 5 to 10 ring atoms, wherein at least one of the ring atoms is a nitrogen atom and any substituent on the ring is as defined as for Formula (I). Particularly preferred Ar groups include pyridyl or indolyl.

A second preferred group of compounds of Formula (I) are those wherein Ar represents a substituted or unsubstituted (preferably aromatic), carbocyclic group, said carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, and any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group.

For the compounds of Formula (I), any substituents on the Ar group are preferably selected from the group consisting of: $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $-OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined as above for Formula (I). R^{10} and R^{11} preferably represent a saturated or unsaturated C_{1-6} straight chain or branched hydrocarbyl group, in particular methyl, ethyl, n-propyl or isopropyl.

Of this preferred class, Ar is preferably substituted with one or more OR^{10} groups,

wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group. An especially preferred R^{10} group is methyl. Particularly preferred Ar groups include phenyl or phenyl substituted with 1, 2 or 3 methoxy groups.

For the preferred class of compounds wherein Ar comprises at least one basic nitrogen function, and wherein Ar represents a carbocyclic ring, the basic nitrogen function is provided by virtue of the carbocyclic ring comprising at least one substituent selected from $NHCOCH_3$ or $N(R^6)(R^8)$, wherein R^6 and R^8 are as defined as for Formula (I).

For the compounds of Formula (I), R preferably represents an unsaturated lower C_{1-6} straight or branched hydrocarbyl group. In particular, R represents $OCH=C(CH_3)_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$ or $OCH_2C\equiv CH$. An especially preferred group of compounds are those wherein Ar is selected from phenyl, trimethoxyphenyl, 3-pyridyl, 4-pyridyl or 3-indolyl and R is selected from $OCH=C(CH_3)_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$ or $OCH_2C\equiv CH$.

For the compounds of Formula (I), R^1 preferably represents a lower C_{1-6} straight or branched hydrocarbyl group, especially methyl.

A further group of preferred compounds of Formula (I) include those wherein:

Ar represents

phenyl, which may be unsubstituted or substituted by one, two or three substituents independently selected from

Cl, Br, F, OMe, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), NMe_2, NEt_2, SCH_3 and $NHCOCH_3$;

thienyl, 2-furyl, 3-pyridyl, 4-pyridyl or indolyl.

R represents

OH or OCH_2R^1, wherein R^1 is selected from $-CH=CMe_2$, $-CMe=CH_2$, $-CH=CH_2$ and $-C\equiv CH$.

It will be appreciated that compounds of Formula (I) which contain a basic amino function may be converted to acid addition salts, with pharmacologically acceptable acids, e.g. hydrochloric acid and phosphoric acid. Such salts are also included in the present invention.

The present invention also provides the use of a compound of Formula (I) in the manufacture of an antiproliferative medicament. In particular, the compounds of the present invention may be useful for the manufacture of a medicament for the treatment or prevention of neoplasms, particularly those located in the uterus, ovary or breast. In particular, the compounds may be useful for the manufacture of a medicament for the treatment of cancer cells that are resistant to paclitaxel and docetaxel.

The compounds of Formula (I) may advantageously be used in combination therapies involving the combined use of a compound of Formula (I) and another anti-neoplastic agent, especially paclitaxel or docetaxel. The combination therapy may involve simultaneous or successive administration of a compound of Formula (I) and an anti-neoplastic agent. Such combination therapy forms a further aspect of the invention.

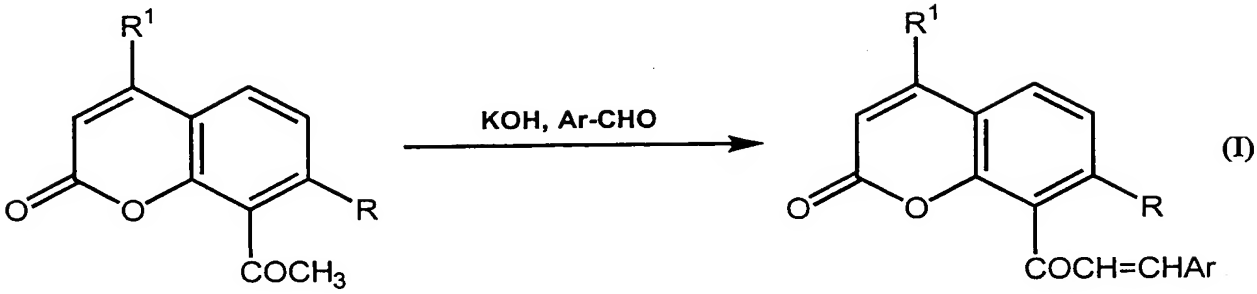
The compounds of the invention may be further used in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.

The present invention further includes a pharmaceutical composition comprising one of more of the compounds of Formula (I) in combination with one or more pharmaceutically acceptable excipients.

The invention will now be described by way of illustrative examples and with reference to the accompanying formulae drawings.

EXAMPLES

Example 1. - General conditions to obtain chalcones.



(I)

Method A.

A solution of KOH 50% (3 ml) is added to an equimolar solution of a ketone (0.0075 mol) and an aldehyde (0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compounds are crystallized by ethanol or first separated by chromatography and then crystallized by ethanol.

Method B.

A solution of a ketone (0.0075 mol), an aldehyde (0.0075 mol), piperidine (15 ml) and acetic acid (75 ml) in ethyl alcohol 95% (80 ml) is countercurrent heated for 5 hours. Molecular sieves are added to the solution to eliminate water and the whole is left at rest for one night. The precipitate that is generally obtained is gathered and crystallized. If the product does not precipitate in these conditions, the solvent is vacuum evaporated and the residue is purified by chromatography on silica gel column.

Example 2. 1-[4-Methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-(pyridin -3-yl)-propen-1-one (see accompanying formula drawing VIB 106).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-(3-methylbut-2-enyloxy)-8-acetylcoumarin (2.14 g, 0.0075 mol) and pyridin-3-carboxy-aldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 0.84 g of product m.p. 156-157°C, ^{1}H-NMR ($CDCl_3$) δ: 1.69 (s, 3H); 1.72 (s, 3H); 2.44 (d, 3H, J = 1.22 Hz); 4.65 (d, 2H, J = 6.5 Hz); 5.34-5.38 (m, 1H); 6.16 (d, 1H, J = 1.2 Hz); 6.95 (d, 1H, J = 8.8 Hz); 7.07 (d, 1H, J = 18 Hz); 7.36 (d, 1H); 7.30-7.40 (m, 1H); 7.64 (d, 1H, J = 8.9 Hz); 7.90 (m, 1H); 8.58 - 8.68 (m, 2H).

Example 3. 1-[4-Methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-phenyl-propen-1-one (see accompanying formula drawing VIB 119).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-(3-methylbut-2-enyloxy)-8-acetylcoumarin (2.14 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 1.34 g of product m.p. 114-16°C, ^{1}H-NMR ($CDCl_3$) δ: 1.69 (s, 3H); 1.72 (s, 3H); 2.44 (d, 3H, J = 1.22 Hz); 4.65 (d, 2H, J = 6.5 Hz); 5.34-5.38 (m, 1H); 6.16 (d, 1H, J= 1.2 Hz); 6.95 (d, 1H, J = 8.8 Hz); 7.00 (d, 1H, J = 18 Hz); 7.10 (d, 1H); 7.30-7.40 (m, 3H); 7.45 -7.52 (m, 12H); 7.61 (d, 1H, J = 8.9 Hz).

Example 4. 1-[4-Methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxyphenyl)propen-1-one (see accompanying formula drawing VIB 120).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-(3-methylbut-2-enyloxy)-8-acetylcoumarin (2.14 g, 0.0075 mol) and 3,4,5-trimethoxybenzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.3 g of product m.p. 148-150°C, ^{1}H-NMR ($CDCl_3$) δ: 1.69 (s, 3H,); 1.72 (s, 3H); 2.44 (d, 3H, J = 1.2 Hz); 3.74 - 3.88 (m, 9H); 4.65 (d, 2H, J = 6.5 Hz); 5.34-5.38 (m, 1H); 6.16 (s, 1H); 6.93 (d, 1H, J = 16 Hz); 6.95 (d, 1H, J = 8.9 Hz); 7.25 (d, 1H, J = 16 Hz); 7.63 (d, 1H, J = 8.9 Hz).

Example 5. 1-[4-Methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(pyridine-3-yl)-propen-1-one (see accompanying formula drawing VIB 122).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-methylallyloxy-8-acetylcoumarin (2.04 g, 0.0075 mol) and pyridin-3-carboxyaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 0.8 g of product m.p. 110-12°C, ^{1}H-NMR ($CDCl_3$) δ: 1.74 (s, 3H); 2.43 (s, 3H); 4.55 (s, 2H); 4.98 (d, 2H, J = 15 Hz); 6,16 (s, 1H); 6.93 (d, 1H, J = 8.9 Hz); 7.09 (d, 1H, J = 16 Hz); 7.35-7.37 (m, 1H); 7.36 (d, 1H, J = 16 Hz); 7.64 (d, 1H, J = 8.9 Hz); 7.85 (d, 1H, J = 7 Hz); 8.58 (d, 1H, J = 5 Hz); 8.67 (s, 1H).

Example 6. 1-[4-Methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-phenyl-propen-1-one (see accompanying formula drawing VIB 121).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-methylallyloxy-8-acetylcoumarin (2.04 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.2 g of product m.p.158-160°C, ^{1}H-NMR ($CDCl_3$) δ: 1.74 (s, 3H); 2.43 (s, 3H); 4.55 (s, 2H); 4.98 (d, 2H, J = 15 Hz); 6,16 (s, 1H); 6.93 (d, 1H, J = 8;9 Hz); 7.02 (d, 1H, J = 16 Hz); 7.43-7.53 (m, 4H); 7.61 (d, 1H, J = 8.9 Hz).

Example 7. 1-[4-Methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(3-methoxy-phenyl)-propen-1-one (see accompanying formula drawing VIB 162).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-methylallyloxy-8-acetylcoumarin (2.04 g, 0.0075 mol) and 3-methoxybenzaldehyde (1.01 g, 0.0075mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.6 g of product m.p. 85-87°C, ^{1}H-NMR ($CDCl_3$) δ: 1.74 (s, 3H); 2.43 (s, 3H); 3.85-3.88 (m, 3H); 4.55 (s, 2H); 4.98 (d, 2H, J = 15 Hz); 6,16 (s, 1H); 6.93 (d, 1H, J = 8.9 Hz; 7.02 (d, 1H, J = 16 Hz); 6.95 -7.12 (m, 3H); 7.26 (m, 1H); 7.30 (d, 1H, J = 16 Hz); -7.61 (d, 1H, J = 8.9 Hz).

Example 8. 1-[4-Methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxy-phenyl)-propen-1-one (see accompanying formula drawing VIB 123).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-methylallyloxy-8-acetylcoumarin (2.04 g, 0.0075 mol) and 3,4,5-trimethoxy-benzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed

under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.7 g of product m.p. 128-130°C, ^{1}H-NMR ($CDCl_3$) δ: 1.74 (s, 3H); 2.43 (s, 3H); 3.75- 3.88 (m, 9H); 4.55 (s, 2H); 4.98 (d, 2H, J = 15 Hz); 6,16 (s, 1H); 6.72 (s, 1H); 6.93 (d, 1H, J = 8.9 Hz); 6.94 (d, 1H, J = 16 Hz); 7.23(d, 1H, J = 16 Hz); 7.61 (d, 1H, J = 8.9 Hz).

Example 9. 1-[4-Methyl-7-(allyloxy)coumarin-8-yl]-3-phenyl-propen-1-one (see accompanying formula drawing VIB 158)

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-allyloxy-8-acetylcoumarin (1.93 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.1 g of product m.p. 136-139°C, ^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H); 4.65 (d, 2H, J = 5.1 Hz); 4.25-4.55 (m, 2H); 5.15- 5.35 (m, 1H); 6,16 (s, 1H); 6.93 (d, 1H, J = 8.9 Hz); 7.03 (d, 1H, J = 16 Hz); 7.04 - 7.15 (m, 3H); 7.15 – 7.26 (m, 2H); 7.33 (d, 1H, J = 16 Hz); 7.64 (d, 1H, J = 8.9Hz).

Example 10. 1-[4-Methyl-7-(allyloxy)coumarin-8-yl]-3-(pyridin-3-yl)-propen-1-one. (see accompanying formula drawing VIB 161).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-allyloxy-8-acetylcoumarin (1.93 g, 0.0075 mol) and pyridin-3-carboxyaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 0.6 g of product m.p. 124-126°C, ^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H); 4.65 (d, 2H, J = 5.1 Hz); 4.25-

4.55 (m, 2H); 5.15 - 5.35 (m, 1H); 6.16 (s, 1H); 6.93 (d, 1H, J = 8.9 Hz); 7.08 (d, 1H, J = 16 Hz); 7.30 (d, 1H, J = 16 Hz); 7.49 (d, 1H, J = 8.9 Hz); 7.83-7.87 (m, 1H); 8.58 (d, 1H, J = 5 Hz); 6.87 (s, 1H).

Example 11. 1 - [4-Methyl-7-(allyloxy)coumarin-8-yl] -3-(3-methoxyphenyl)-propen-1-one (see accompanying formula drawing VIB 159).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-allyloxy-8-acetylcoumarin (1.93 g, 0.0075 mol) and 3-methoxybenzaldehyde (1.01 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.6 g of product m.p. 61-63°C ^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H); 3.82 (s, 3H); 4.65 (d, 2H, J = 5.1 Hz); 5.20-5.42 (m, 2H); 5.82-6.02 (m, 1H); 6,16 (s, 1H); 6.90 (d, 1H, J = 8,9 Hz); 7.15 (d, 1H, J = 16 Hz); 6.90-7.15 (m, 3H); 7.15 (d, 1H, J = 16 Hz); 7.20-7.29 (m, 1H); 7.30 (d, 1H, J = 16 Hz); 7.64 (d, 1H, J = 8.9 Hz).

Example 12. 1-[4-Methyl-7-(allyloxy)coumarin-3-yl]-3-(3,4,5-trimethoxyphenyl)-propen-1-one (see accompanying formula drawing VIB 160).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-allyloxy-8-acetylcoumarin (1.93 g, 0.0075 mol) and 3-methoxybenzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.8 g of product m.p. 138-140°C ^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H); 3.82 -3.91 (m, 9H); 4.65 (d, 2H, J = 5.1 Hz); 5.25 - 5.40 (m, 2H); 5.90 - 6.02 (m, 1H); 6.16 (s, 1H); 6.74 (s, 2H); 6.90-7.15 (m, 3H); 7.15 (d, 1H, J = 16 Hz); 7.20 - 7.29 (d, 1H, J = 16 Hz); 7.70(d, 1H, J = 8.9).

Example 13. 1-[4-Methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxy-phenyl)-propen-1-one (see accompanying formula drawing VIB 126).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-prop-2-ynyloxy-8-acetylcoumarin (1.92 g, 0.0075 mol) and 3,4,5-trimethoxy-benzaldehyde (1.47 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 1.1 g of product m.p. 191-93°C, ^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H); 2.53-2.56 (m, 1H); 3.83-3.85 (m, 9H); 4.82 (d, 2H, J = 2.2 Hz); 6.20 (s, 1H); 6.72 (s, 2H); 6.92 (d, 1H, J = 16 Hz); 7.12 (d, 1H, J = 8.9 Hz); 7.15 (d, 1H, J = 16 Hz); 7.67 (d, 1H, J = 8.9 Hz).

Example 14. 1-[4-Methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-phenylpropen-1-one (see accompanying formula drawing VIB 124).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-prop-2-ynyloxy-8-acetylcoumarin (1.92 g, 0.0075 mol) and benzaldehyde (0.8 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 0.8 g of product m.p. 140-42°C, ^{1}H-NMR ($CDCl_3$) δ : 2.45 (s, 3H); 2.53-2.56 (m, 1H); 4.82 (d, 2H, J = 2.2 Hz); 6.20 (s, 1H); 7.02 (d, 1H, J = 16 Hz); 7;13 (d, 1H, J -=8.9 Hz); 7.32 (d, 1H, J = 16 Hz); 7.35 -7.45 (m, 3H); 7.48 - 7.52 (m, 2H); 7.67 (d, 1H, J = 8.9 Hz).

Example 15. 1-[4-Methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(pyridin-3-yl)-propen-1-one (see accompanying formula drawing VIB 125).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-prop-2-ynyloxy-8-acetylcoumarin (1.92 g, 0.0075 mol) and pyridin-3-carboxy aldehyde (0.8 g,

0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 0.7 g of product m.p. 203-205°C, ^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H); 2.53-2.56 (m, 1H); 4.82 (d 2H, J = 2.2 Hz); 6.20 (s, 1H); 7.02 (d, 1H, J = 16 Hz); 7.13 (d, 1H, J = 8.9 Hz; 7.32 (d, 1H, J = 16 Hz); 7.28-7.35 (m, 1H); 7.69 (d, 1H, J = 8.9 Hz); 7.88 - 7.92 (m, 1H); 8.58 - 8.62 (m, 1H); 8.66 (s, 1H).

Example 16. 1-[4-Methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(3-methoxyphenyl)-propen-1-one (see accompanying formula drawing VIB 163).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-prop-2-ynyloxy-8-acetylcoumarin (1.92 g, 0.0075 mol) and 3-methoxybenzaldehyde (1.01 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified. The precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.5 g of product m.p. 154-56°C, ^{1}H-NMR ($CDCl_3$) δ: 2.45 (s, 3H); 3.48 (m, 1H; 3.81 (s, 3H); 4.82 (d, 2H, J = 2.2 Hz); 6.15 (s, 1H); 6.90 - 7.26 (m, 5H); 7.10 (d, 1H, J = 8.9 Hz); 7.65 (d, 1H, J = 8.9 Hz).

Example 17. 1-[4-Methyl-7-(allyloxy)coumarin-8-yl]-3-(4-chlorophenyl)-propen-1-one (see accompanying formula drawing VIB 241).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-allyloxy-8-acetylcoumarin (1.93 g, 0.0075 mol) and 4-chlorobenzaldehyde (1.05 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.1 g of product m.p. 153-155°C, ^{1}H-NMR ($CDCl_3$) δ: 2.42 (d, J=1.2 Hz, 3H), 4.65 (m, 2H), 5.2 (m, 2H), 6.15 (m, 1H), 6.91-7.61 (m, 8H).

Example 18. 1-[4-Methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(4-fluoro-phenyl)-propen-1-one (see accompanying formula drawing VIB 240).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-prop-2-ynyloxy-8-acetylcoumarin (1.92 g, 0.0075 mol) and 4-fluorobenzaldehyde (0.93 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by ethanol to give 1.2 g of product m.p. 185-186°C, ^{1}H-NMR ($CDCl_3$) δ: 2.43 (d, J=1.2 Hz, 3H), 2.52 (m, 1H), 4.79 (d, J=1.2 Hz, 2H), 6.17 (d, J=1.2 Hz, 1H), 6.96-7.66 (m, 8H).

Example 19. 1-[3-methyl-7-methoxy)coumarin-8-yl]-3-(2-thienyl)-propen-1-one (see accompanying formula drawing VIB 242).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 7-methoxy-8-acetyl-3-methylcoumarine (1.74 g, 0.0075 mol) and 2-thio-phenecarboxyaldehyde (0.84 g, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.8 g of product m.p. 172-173°C, ^{1}H-NMR ($CDCl_3$) δ: 2.46 (d, 3H), 4.0 (s, 3H), 6.21 (d, J=1.2 Hz, 1H), 6.91-7.84 (m, 7H).

Example 20. 1-[4-Methyl-7-(allyloxy)coumarin-8-yl]-3-(2,6-dichloro-phenyl)-propen-1-one (see accompanying formula drawing VIB 243).

A solution of KOH 50% (3 ml) is added to an equimolar solution of 4-methyl-7-allyloxy-8-acetylcoumarin (1.93 g, 0.0075 mol) and 2,6-dichlorobenzaldehyde (1.31ág, 0.0075 mol) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. The compound is crystallized by methanol to give 1.1 g of product m.p. 149-151°C, ^{1}H-NMR ($CDCl_3$) δ: 2.41 (m, 3H), 4.66 (m, 2H), 5.3 (m, 2H), 5.9 (m, 1H), 6.9-7.64 (m, 8H).

BIOLOGICAL EVALUATION

Compounds VIB 106 and VIB 122 were tested for their cytotoxicity against drug-resistant cancer cells, both alone, and in combination with paclitaxel. The results of these studies are shown below.

When tested alone, compounds VIB 106 and VIB 122 were found to possess relatively low cytotoxicity (IC_{50} > 1 μM) against drug-resistant cancer cells.

The compounds were then evaluated in combination with paclitaxel for their cytostatic activity against the drug-resistant breast cancer cells MDA-435/LCC6-MDR. In the experiments, the compounds were used in combination with paclitaxel, the paclitaxel being at a concentration of 0.1 μM, the IC_{50} of paclitaxel decreases by 3-5 fold when used in combination with each of compounds VIB 106 and VIB 122, i.e. from 426 nM to 130-86 nM compared with paclitaxel alone. Consequently, in the presence of these compounds, paclitaxel can recover its excellent inhibitory activities against the drug-resistant cancer cells.

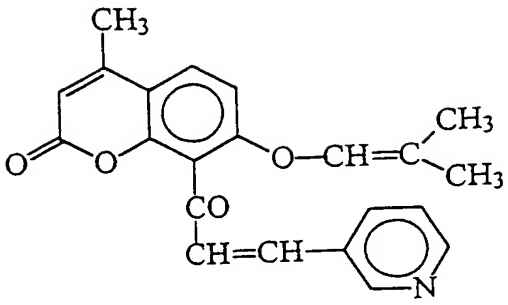
Compound	IC_{50}/nM	% Reduction in IC_{50} of paclitaxel
Paclitaxel	426	-
VIB 106 + Paclitaxel	86	80
VIB 122 + Paclitaxel	130	70

Table 1

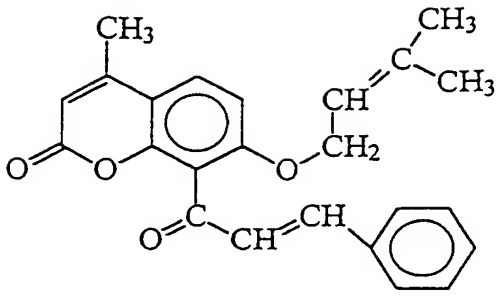
Experimental

The treatment consisted of concurrent exposure of MDA-435/LCC-MDR cells to paclitaxel in the presence or absence of the compounds reversing agent (1 μM) for 72 h *in vitro*. Assessment of cytotoxicity, i.e. cell growth inhibition, was determined according to the methods of Skehan, et al. as discussed in J. Nat. Cancer Inst., 82, 1107, 1990.

Briefly, cells were plated between 400 and 1200 cells/well in 96 well plates and incubated at 37°C for 15-18 h prior to drug addiction to allow attachment of cells. Compounds were solubilized in 100% DMSO and further diluted in RPMI-1640 containing 10 mM HEPES. After a 72 h incubation, 100 ml of ice-cold 50% TCA was added to each well and incubated for 1 h at 4°C. Plates were then washed 5 times with tap water to remove TCA, low-molecular weight metabolites and serum proteins. Sulforhodamine B (SRB) (0.4%, 50 ml) was added to each well. Following a five minute incubation at room temperature, plates were rinsed 5 times with 0.1% acetic acid and air dried. Bound dye was solubilized with 10 mM Tris Base (pH 10.5) for 5 min on a gyratory shaker. Optical density was measured at 570 nm.



VIB 106



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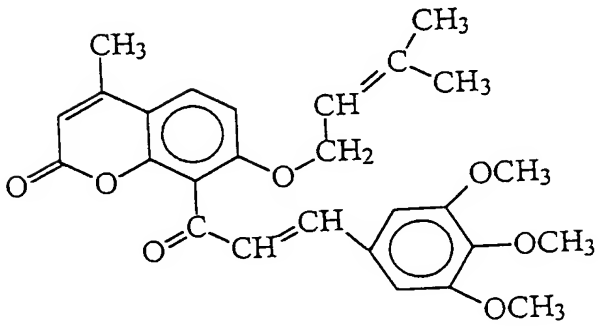

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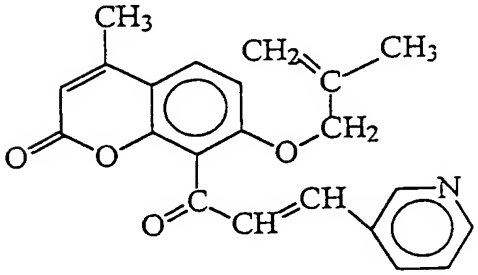

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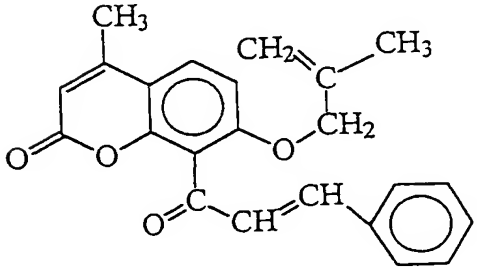

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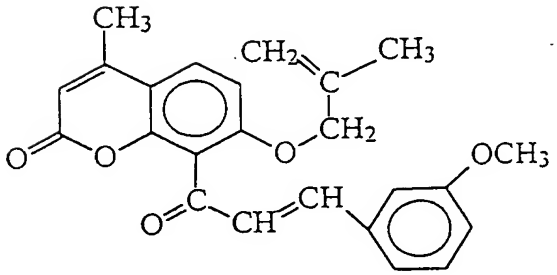

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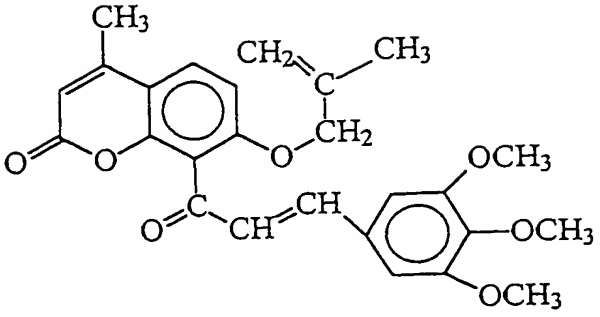

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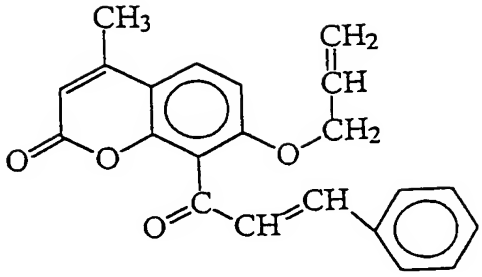
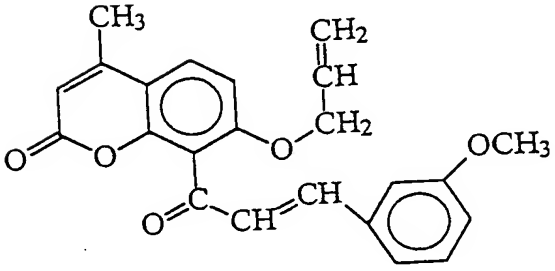


VIB 158



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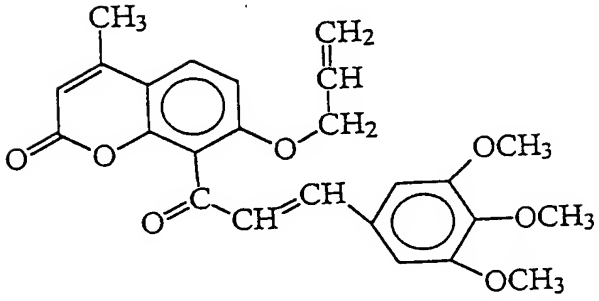

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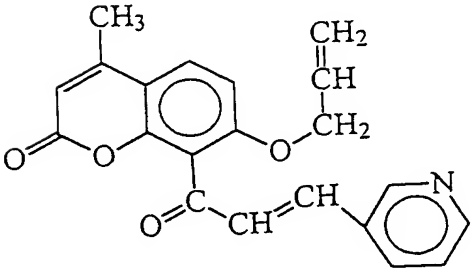

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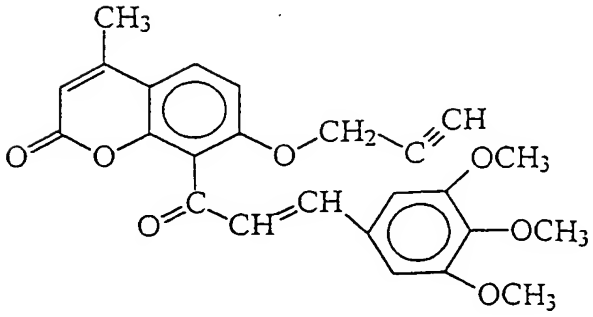

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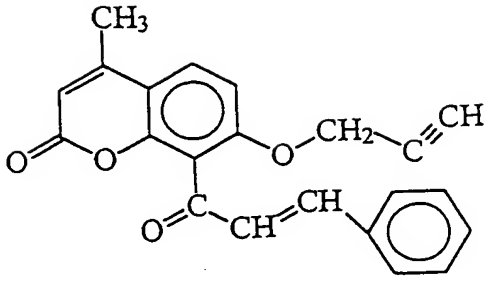

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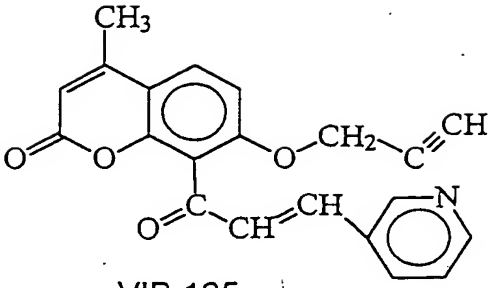

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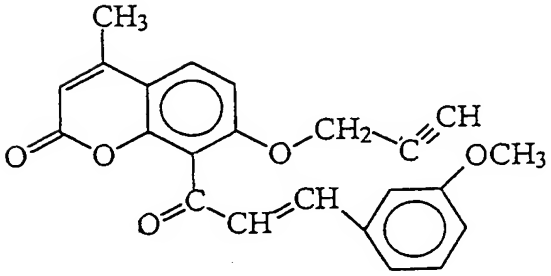

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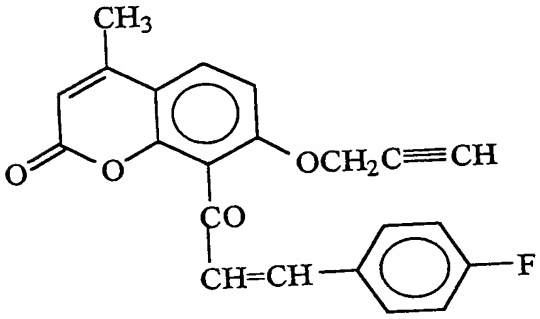

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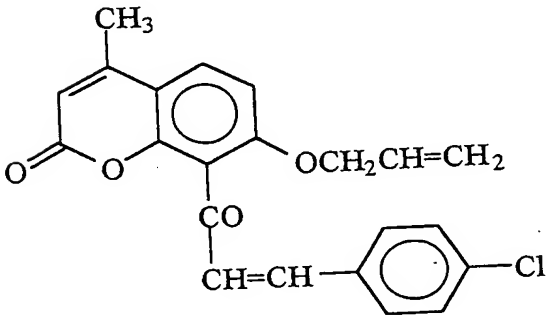

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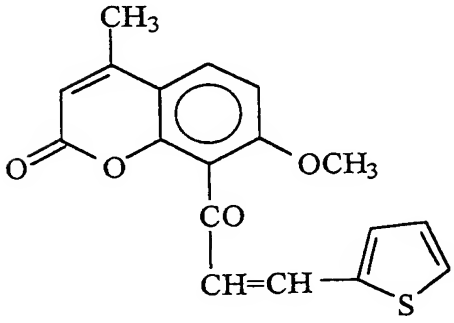

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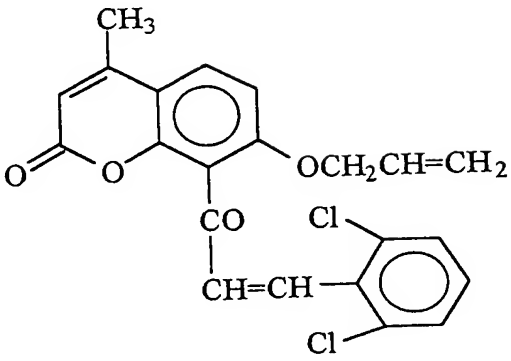
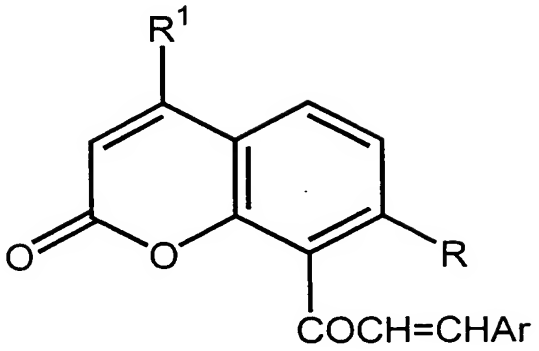


VIB 243

CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof wherein:

Ar represents:

a substituted or unsubstituted, (preferably aromatic), carbocyclic or heterocyclic group, said carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group;

R represents

OH, OR^{10} or $OCOR^{11}$, wherein R^{10} and R^{11} are as defined above; and

R^1 represents H or a lower C_{1-6} straight or branched hydrocarbyl group which may be

unsubstituted or substituted by 1, 2 or 3 substituents selected from Cl, Br, F, OMe, NO_2 and CF_3.

2. A compound according to Claim 1 wherein Ar represents a substituted or unsubstituted (preferably aromatic), heterocyclic group said heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein the or each ring contains 5 or 6 ring atoms, the heteroatoms being selected from N, O and S, and any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group.

3. A compound according to any preceding claim wherein the Ar group is a substituted or unsubstituted (preferably aromatic), heterocyclic group, said heterocyclic group containing from 5 to 10 ring atoms, wherein at least one of the ring atoms is a nitrogen atom and any substituent on the ring is as defined as for Claim 1.

4. A compound according to any preceding claim wherein Ar represents pyridyl or indolyl.

5. A compound according to Claim 1 wherein Ar represents a substituted or unsubstituted (preferably aromatic), carbocyclic group, said carbocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein

the or each ring contains 5 or 6 ring atoms, and any substituents on the Ar group being independently selected from the group consisting of:

(a) Cl, (b) Br, (c) F, (d) OH, (e) NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R^6)(R^8)$ wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl, (k) OR^{10} wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from:

Cl, Br, F, OMe, NO_2 and CF_3,

and (l) $-OCOR^{11}$, wherein R^{11} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group or a phenyl group.

6. A compound according to any preceding claim wherein any substituents on the Ar group are selected from the group consisting of: $NHCOCH_3$, $N(R^6)(R^8)$, OR^{10} and $-OCOR^{11}$, wherein R^6, R^8, R^{10} and R^{11} are as defined in Claim 1.

7. A compound according to any preceding claim wherein Ar is substituted with one or more OR^{10} groups, wherein R^{10} represents a saturated or unsaturated lower C_{1-6} straight or branched hydrocarbyl group.

8. A compound according to Claim 7 wherein R^{10} represents methyl.

9. A compound according to any of Claims 5 to 8 wherein Ar is selected from phenyl or phenyl substituted with 1, 2 or 3 methoxy groups.

10. A compound according to any preceding claim wherein R represents an unsaturated lower C_{1-6} straight or branched hydrocarbyl group.

11. A compound according to Claim 10 wherein R represents $OCH=C(CH_3)_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$ or $OCH_2C\equiv CH$.

12. A compound according to Claim 1 wherein Ar is selected from phenyl, trimethoxyphenyl, 3-pyridyl, 4-pyridyl or 3-indolyl; and R is selected from $OCH=C(CH_3)_2$, $OCH_2CMe=CH_2$, $OCH_2CH=CH_2$ or $OCH_2C\equiv CH$.

13. A compound according to any preceding claim wherein R^1 represents a lower C_{1-6} straight or branched hydrocarbyl group.

14. A compound according to Claim 13 wherein R^1 represents methyl.

15. A compound according to Claim 5 wherein:

Ar represents

phenyl, which may be unsubstituted or substituted by one, two or three substituents independently selected from

Cl, Br, F, OMe, NO_2, CF_3, C_{1-4} lower alkyl (in particular CH_3), NMe_2, NEt_2, SCH_3 and $NHCOCH_3$;

thienyl, 2-furyl, 3-pyridyl, 4-pyridyl or indolyl.

R represents

OH or OCH_2R^1, wherein R^1 is selected from $-CH=CMe_2$, $-CMe=CH_2$, $-CH=CH_2$ and $-C\equiv CH$.

16. A compound according to any preceding claim wherein R^6 and R^8 are the same or different and each represents H or lower C_{1-4} alkyl.

17. A compound according to any preceding claim wherein R^{10} and R^{11} represents a saturated or unsaturated C_{1-6} straight chain or branched hydrocarbyl group.

18. A compound according to any Claim 17 wherein R^{10} and R^{11} are selected from methyl, ethyl, n-propyl or isopropyl.

19. A compound of Formula (I) selected from the following:

1-[4-methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-(pyridine-3-yl)propen-1-one (VIB 106),

1-[4-methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-phenylpropen-1-one (VIB 119),

1-[4-methyl-7-(3-methylbut-2-enyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxyphenyl)-propen-1-one (VIB 120),

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(pyridine-3-yl)propen-1-one VIB 122),

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-phenylpropen-1-one (VIB 121),

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(3-methoxyphenyl)propen-1-one (VIB 162),

1-[4-methyl-7-(2-methylallyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxyphenyl)propen-1-one (VIB 123),

1-[4-methyl-7-(allyloxy)coumarin-8-yl]-3-phenylpropen-1-one (VIB 158),

1-[4-methyl-7-(allyloxy)coumarin-8-yl]-3-(pyridin-3-yl)propen-1-one (VIB 161),

1-[4-methyl-7-(allyloxy)coumarin-8-yl]-3-(3-methoxyphenyl)propen-1-one (VIB 159),

1-[4-methyl-7-(allyloxy)coumarin-3-yl]-3-(3,4,5-trimethoxyphenyl)propen-1-one (VIB 160),

1-[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(3,4,5-trimethoxyphenyl)propen-1-one (VIB 126),

1-[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-phenylpropen-1-one (VIB 124),

1-[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(pyridin-3-yl)propen-1-one (VIB 125), and

1-[4-methyl-7-(prop-2-ynyloxy)coumarin-8-yl]-3-(3-methoxyphenyl)propen-1-one (VIB 163).

20. A compound of Formula (I) as defined in any preceding claim for use as a antiproliferative medicament.

21. Use of a compound of Formula (I) as defined in any preceding claim for the manufacture of a medicament for the treatment or prevention of neoplasms.

22. Use according to Claim 21 wherein the neoplasms are located in the uterus, ovary or breast.

23. Use according to Claim 21 or 22 of a compound of Formula (I) for the manufacture of a medicament for the treatment of paclitaxel- and docetaxel-resistant cancer cells.

24. Use according to any of Claims 21 to 23 of a compound of Formula (I) in the manufacture of an antiproliferative medicament for combination therapy.

25. Use according to Claim 24 of a compound of Formula (I) in the manufacture of an antiproliferative medicament in combination with one or more antineoplastic agents.

26. The use according to Claim 25 wherein the antineoplastic agent comprises paclitaxel or docetaxel.

27. The use according to Claim 19 in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.

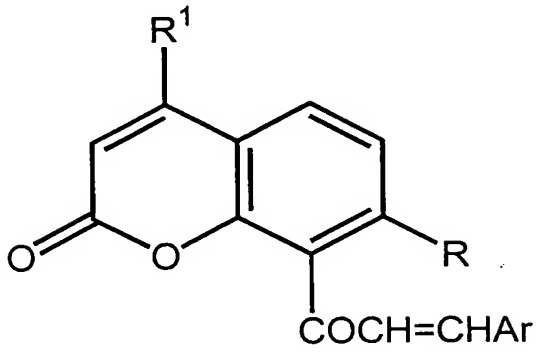
28. A pharmaceutical composition comprising one of more of the compounds of Formula (I) as defined in any preceding claim, in combination with one or more pharmaceutically acceptable excipients.

29. A pharmaceutical composition according to Claim 28 further comprising one or more antineoplastic agents.

30. A pharmaceutical composition according to Claim 29 wherein the antineoplastic agent is selected from paclitaxel or docetaxel.

ABSTRACT

Disclosed are novel chalcone derivatives having the Formula (I):



(I)

The compounds possess antiproliferative activity, and are useful for the manufacture of a medicament for the treatment or prevention of neoplasms, particularly those located in the uterus, ovary or breast. The compounds of the invention may also be useful in the manufacture of a medicament for the treatment or prevention of menopausal disorders and osteoporosis.